Fish oil dietary supplements: a clinician's point of view

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Abstract

There are two main types of omega-3 products: Fish oil dietary supplements (FODS) and prescription Omega 3 products. There are few non-fish oil omega 3 supplements. Currently available omega-3 (OM-3) fatty acid products in Sri Lanka are mostly nonprescription fish oil dietary supplements (FODS). The 'prescription OM-3 drugs' are not registered in Sri Lanka at present. Prescription OM-3 products are indicated in adults with severe hypertriglyceridemia. The National Medicines Drug Regulatory Authority (NMRA) considers FODS as borderline products. The FODS have issues such as variable content of OM-3, inaccurate labelling, impurities and oxidized fatty acids and poor product quality. Given these issues, FODS should not be substituted for prescription OM-3 products. This review describes the differences between FODS and prescription OM-3 products and highlights some clinically relevant points for a practicing physician regarding FODS in Sri Lanka.

Key words: fish oil, omega 3, dietary supplements, Omega-3-fatty acids; docosahexaenoic acid, eicosapentaenoic acid, icosapent ethyl, hypertriglyceridemia

Introduction

Fish oil dietary supplements (FODS) are prescribed widely in Sri Lanka. As of November 2020, there are 33 varieties of FODS available in the Sri Lankan market. Even when not prescribed, patients take FODS on their own. Most believe taking FODS reduces the risk of heart disease and promotes general health.

There are two main types of omega-3 (OM 3) products: Fish oil dietary supplements (FODS) and prescription Omega 3 products. There are few non-fish oil omega 3 supplements.

Omega-3 fatty acids (FA), one of the polyunsaturated fatty acids (PUFAs) is the main ingredient in FODS. There are different types of omega-3 FAs: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Icosapent ethyl (IPE) is a highly purified form of EPA which is marine-derived. The sources of the three Omega-3 FAs are given in Table 1.

Practice points

1. Fish oil dietary supplements (FODS) are not a substitution for prescription omega 3 products. Conclusive data are lacking about their benefits in many clinical conditions.
2. In a healthy adult with no cardiovascular disease, there is no need of FODS, provided 2-3 servings of fatty fish (kumbalawa, hurulla etc) is ingested per week.
3. If there is intolerance or dislike for fish, a 500-1000 mg dose of a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be taken. (Algae-based supplements if patient is a vegetarian or allergic to fish).
4. If the patient has an elevated serum triglyceride level and a history of cardiovascular disease or major cardiovascular risk factors, a high-dose prescription omega-3 product (EPA+DHA >3g/day) can be used, but it is not a replacement for statins.
5. Advise the patient that no dietary supplement including FODS can substitute for healthy diet and adequate physical activity.

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Table 1. Sources of Omega-3 FAs

Omega-3 FA	Source
ALA	Plant oils, such as flaxseed, soybean, and canola oils
DHA and EPA	Salmon, mackerel, tuna, herring, and sardines anchovies, herring, capelin, and hoki. ¹ Out of fish available in Sri Lanka, small fish such as <i>Rastrelliger kanagurta</i> (Indian mackerel or kumbalawa) is a good source of EPA and <i>Amblygaster sirm</i> (trenched sardinella or hurulla) is a good source of DHA. ² Other locally available fatty fish are halmessa, karalla, linna, hunu ranna, silava and alagoduwa.

ALA is considered an essential FA as the human body cannot synthesize it and humans must obtain it from the diet. EPA and DHA can be produced from ALA in the human body but the conversion is limited. Therefore, food and dietary supplements are the main sources of EPA and DHA.^{1,3,4} Some food items such as eggs (by feeding hens with omega rich food) and milk have been fortified with omega-3 (OM-3).

Amount of Omega-3 (OM-3)

Authorities differ in the amounts of EPA+DHA recommended as daily dosage.⁵ Based on the Global Organization for EPA & DHA omega-3s (GOED), recommendation for most healthy adults is 500 mg of EPA+DHA and for secondary prevention of CVD 1000mg is recommended.⁶

Difference between FODS and prescription omega-3 products

Prescription OM-3 products are drugs which contain high doses of omega-3. Generally, prescription OM-3 products contain >3g of EPA+DHA. FODS are considered dietary supplements. Omega-3 fatty acids is the active ingredient in FODS. The FODS are not governed by the same regulatory measurements as 'prescription OM-3 drugs' by the FDA in the USA and the NMRA in Sri Lanka. The amount of EPA and DHA in FODS are variable. Prescription OM-3 (3 g/d total EPA+DHA) have higher EPA and DHA than FODS whereas FODS have varying amounts of EPA+DHA but usually less than 2 grams.

Guideline recommendations for the use of prescription omega-3

The National Lipid Association (NLA) of United States of America, recommends for patients with fasting triglycerides 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy ($\pm$ ezetimibe), aged ≥ 45 years with clinical ASCVD, or aged ≥ 50 years

with diabetes mellitus requiring medication plus ≥ 1 additional risk factor, treatment with icosapent ethyl (IPE) for ASCVD risk reduction.⁷ The ESC 2019 dyslipidaemia guidelines also recommend, in high-risk (or above) patients with TG between 135-499 mg/dL (1.5 and 5.6 mmol/L) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 g/day) should be considered in combination with statins.⁸ Both these recommendations were after the results of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) trial. The REDUCE-IT trial used icosapent ethyl (IPE). It concluded that IPE 4 g/d reduced by 25%, the first major adverse cardiovascular event (cardiovascular death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina) in selected high or very high-risk, statin-treated patients with elevated triglycerides.

Cardiovascular effects of omega 3 fatty acids

There is conflicting evidence regarding OM-3's role in prevention of CVD. AHA science advisory in 2017 recommended OM-3 for use in those with established coronary heart disease (e.g., past myocardial infarction). It was considered reasonable for a potential modest benefit.⁹ It is said that doses of <2 g/d EPA+DHA are not effective for reducing triglyceride.^{8,10} In contrast, the NICE 2020 guidelines recommend not offering OM-3 products to prevent CVD.¹¹

A Cochrane review including 86 trials involving 162,796 people done in 2020 (evaluating evidence up to Feb 2019) concluded, moderate- and low-certainty evidence suggests that increasing long-chain omega-3 (LCn3), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) slightly reduces the risk of coronary heart disease mortality and events and reduces serum triglycerides (evidence mainly from supplement trials) but the supplements did not affect all-cause mortality, cardiovascular events, stroke, or arrhythmia.¹²

Non Cardiovascular benefits of OM-3

Despite popular belief that OM-3 supplements are useful in a variety of clinical conditions, the data is not conclusive.¹⁰ A review analyzing 47 long-term RCTs found that increasing long-chain omega 3, probably has little or no effect on the risk of cancer diagnosis, cancer death or breast cancer diagnosis but may slightly increase prostate cancer risk (NNT 334).¹² OM-3 dietary supplementation for arthritis noted a moderate benefit in rheumatoid arthritis, but insufficient evidence to determine the effect in other types of arthritides.¹⁰ It is said to improve cognition in very mild Alzheimer's disease (AD) but it is not recommended as a treatment of AD.¹³ A meta-analysis of three high-quality randomized controlled trials in cognitively healthy patients concluded that OM-3 dietary supplementation did not improve cognitive function.¹⁴ RCTs done on age-related macular degeneration (AMD) failed to show a decreased risk of advanced AMD development.¹⁵

Practical problems of FODS

As FODS are only dietary supplements and they are not under the same regulations such as prescription OM 3. Therefore, the chemical composition, integrity and purity are not verified. There are differences between measured amounts of EPA and DHA in FODS than what they claim to have.¹⁶ FODS contain OM-3 FA and saturated fats. Studies done in USA and New Zealand have shown FODS to contain high levels of oxidized lipids, an indication of lipid decomposition.^{17,18} As FODS contain varying levels of fatty acids, saturated fats and lipid oxidation products, there are health concerns about them. The oxidation products interfere with the antioxidant activity of the FODS and saturated fatty acids increase cardiovascular risk.¹⁹

The FDA states, all FODS carrying any statement regarding health benefits must carry a disclaimer stating that the claim "has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease". The FDA also approved a qualified health claim for FODS that contain EPA and DHA.^{20,21} This health claim states, "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 FAs may reduce the risk of coronary heart disease."

There are several drug interactions with FODS. The clinically relevant drug interactions are with oral anticoagulants. FODS are considered safe when used with warfarin or antiplatelets if used <3g/day despite concerns regarding increased bleeding risk.²²

Side effects of FODS

Commonly reported side effects include unpleasant taste, fishy breath, nausea, gastrointestinal discomfort, diarrhea and headache.

How to choose a FODS

When selecting a FODS, it is always good to look for a good quality manufacturer. The next step would be to look for endorsements by regulatory authorities (if sourced from overseas). After selecting the FODS, to decide on the dosage, one needs to look in to the amounts of EPA and DHA in one serving and how many capsule/soft gels to ingest to obtain the amount of OM-3 specified.

FODS in Sri Lanka

All FODS sold in the country must be registered with the NMRA. Some FODS are registered as medicines and some as borderline products, but according to the newest regulations all FODS have to be registered as borderline products. The National Medicines Regulatory Authority Act No. 05 of 2015 the National Medicines Regulatory Authority is responsible for the regulation and control of registration, licensing, manufacture, importation and all other aspects pertaining to borderline products.

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